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EXAMINER	
KUDLA, JOSEPH S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,318	GAMELIN ET AL.	
	Examiner	Art Unit	
	JOSEPH S. KUDLA	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6 and 9-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Foreword

1. Applicants' Amendment-After Non-Final Rejection, amended claim set and amended specification, filed June 13, 2008, are acknowledged. With respect to Applicants' Arguments/Remarks in the correspondence, the arguments and request for reconsideration have been fully considered and found to be partly persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejection and objection are newly applied. They constitute the complete set presently applied to the instant specification. This office action is **FINAL**.

Instant claims 1, 4-6, 9 and 10 have been amended, instant claims 3 and 8 are cancelled and new claim 13 added.

Instant claims 1, 4-6 and 9-13 are presented for examination on the merits as they read upon the elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 6 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the inhibition or prevention of neurotoxicity by administering oxaliplatin with calcium and magnesium; where the

magnesium is dosed in a parenteral dosage form and the calcium is dosed in both an oral and a parenteral dosage form at a time prior to, after, during or in any sequence.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation to treat neurotoxicity.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is broad in scope for the administration schedule of the treatment regimen. Applicant has not provided sufficient evidence to support a claim set drawn to the inhibition or prevention of neurotoxicity by administering oxaliplatin with calcium and magnesium, where the magnesium is dosed in a parenteral dosage form and the calcium is dosed in both an oral and a parenteral dosage form at a time prior to, after, during or in any sequence. Prevention/inhibition of most disorders/conditions/diseases treated by pharmaceutical means remains largely an elusive goal. The breadth of the claims exacerbates the complex nature of the subject matter to which the present claims are directed.

The nature of the invention

The instant claim set outlines two inventions (a composition and a method) wherein prevention or inhibition or treatment of neurotoxicity by administering oxaliplatin with calcium and magnesium, where the magnesium is dosed as a parenteral dosage form and the calcium is dosed in both an oral and a parenteral dosage form at a time prior to, after, during or in any sequence. The instant claims disclose the calcium and magnesium can exist in various salts and the daily dosages to be administered.

The state of the prior art

Prior art in the field shows injectable solutions of calcium and magnesium are administered parenterally, simultaneously or after injection of oxaliplatin to treat neurotoxicity (Laine-Cessac et al.).

The level of predictability in the art

"To prevent", as defined by Merriam-Webster Dictionary is to keep from happening or existing, which implies taking advance measures against something possible or probable. Furthermore, the definition of "to prevent" and the "act of preventing" embraces the complete 100% inhibition. Thus, the burden of enablement in the assertion of this claim is much higher than would be the case of enabling the treatment of the condition and is not achieved. Nowhere in the prior art or instant application has calcium and magnesium, where the magnesium is dosed as a parenteral dosage form and the calcium is dosed in both an oral and a parenteral dosage form at a time prior to, after, during or in any sequence. in the instant claim set been enabled to prevent neurotoxicity.

The existence of this obstacle establishes that the contemporary knowledge in the art would have prevented one of ordinary skill in the art from accepting any therapeutic regimen for the treatment of neurotoxicity with the Applicants' proposed drug regimen on its face. *In re Fisher, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970)*, indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hence, one of skill in the art is unable to fully

predict the ability of an oral formulation of calcium given at any time to prevent or inhibit neurotoxicity for any product that releases oxalate during its metabolism.

The amount of direction provided by the inventor and the existence of working examples

The instant specification does not provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to practice the claimed methods commensurate in the scope with the instant claims. Applicant provides *no* guidance demonstrating the ability of an oral formulation of calcium and magnesium, where the magnesium is dosed as a parenteral dosage form and the calcium is dosed in both an oral and a parenteral dosage form at a time prior to, after, during or in any sequence is able to prevent or inhibit neurotoxicity. Adequate enablement requires more than a mere statement that a compound treats a given condition.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention (*In re Wright, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir. 1993)*). The specification lacks sufficient disclosure to support applicant's claims of the ability of an oral formulation of calcium given at any time to prevent or inhibit neurotoxicity for any product that releases oxalate during its metabolism. There is not seen sufficient working examples or data from references in

the prior art providing a nexus between that which applicant asserts is supporting a method of preventing or inhibiting neurotoxicity with an oral formulation of calcium and the amount of disclosure Applicant has actually provided.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Based on the unpredictable nature of the invention, the state of the prior art and the breadth of the claims, one skilled in the art could not have practiced the claimed invention without undue experimentation. The essential element towards the validation of a therapeutic modality capable of performing the mechanism of action is the ability to test the compound or composition within *specific parameters* in advance of administration of a compound and, while maintaining experimental control, link those results with sampling time points. Once it can be documented that the compound/composition of interest elicits a desired pharmacological response within experimental controls, the compound, for the sake of this forum, could generally be assumed to have that pharmacological activity.

Based on the unpredictable nature of the invention, the state of the prior art and the extreme breadth of the claims, one skilled in the art could not have practiced the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 4-6 and 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," Therapie, Vol. 53 page 183, 1998), in view of Chazard (US Patent Publication US 2002/0045632).

Laine-Cessac et al. teaches that the anticancer agent (line 5) oxaliplatin–induced neurotoxicity (1st sentence) can be dramatically improved after simultaneous (patient

F/49 in table- given 4 minutes after the start of the 2-hour infusion of oxaliplatin) or post-injection (patient F/59 in table—given 15 minutes after the end of the infusion) administration of calcium and magnesium. Patients were intravenously administered a mixture of calcium gluconate and magnesium sulfate (1st sentence below table).

Laine-Cessac et al. does not teach the use of an oral calcium formulation nor the administration dosages or schedules.

Chazard teaches the use of an oral formulation of calcium folinate and an intravenous administration oxaliplatin (paragraph 36) to treat tumors (Abstract). Chazard teaches the calcium folinate is to be administered for 1-14 days (paragraph 36). Chazard also teaches an example (Example 2, pages 3 and 4) calculating the maximal tolerated dose of oxaliplatin with calcium folinate (page 3, paragraph 33). One of the parameters for selection into the study was that the subjects exhibit "no evidence of peripheral neuropathy" (page 3, paragraph 34). Chazard teaches that 19 subjects (page 4, paragraph 38) were treated with up to 130 mg/m^2 of oxaliplatin while being treated with 90 mg/day of calcium folinate (page 3, table after paragraph 5) without experiencing dose limiting toxicity (page 4, paragraph 38).

It would have been obvious to one of ordinary skill in the art, in view of the teachings of Laine-Cessac et al., drawn to a parenteral composition comprising a parenteral drug regimen of oxaliplatin and magnesium and calcium salts in the treatment of adenocarcinoma, and Chazard, drawn to an oral formulation of calcium folinate and an intravenous administration oxaliplatin to treat tumors, a preparation of all of the elements of both formulations would similarly be useful in treating tumors and

alleviating neuropathy. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). Therefore, combining the teachings of Laine-Cessac et al. and Chazard would have resulted in a drug regimen for the treatment of cancer that contained an oral calcium dosage, a parenteral dosage of calcium and magnesium and an active ingredient which releases oxalate during its metabolism (e.g., oxaliplatin).

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, no more than routine experimentation would have been necessary to one of ordinary skill in the art to arrive at both the administration dosages, a dosage schedule (e.g., prior, after, during, sequential, separately, etc.) recited in instant claims 1, 5, 6 and 9-12 and an optimal oral formulation of a calcium salt that would be easily assimilated in the body, as in instant claim 4.

Therefore, the teachings of Laine-Cessac et al., in view of Chazard, render the claimed invention obvious.

Response to ArgumentsA. Applicant contends that the combination of Laine-Cessac et al. and Chazard references destroys the operability of the Chazard reference and makes the invention non-obvious (page 15, paragraph 4 to page 17, paragraph 1 of Applicants' amendment).

Applicant's argument has been fully considered but found not persuasive.

The Chazard reference teaches that of the 13 patients evaluated for treatment efficacy, nine have achieved a stable disease with the drug regime that includes an oral calcium salt and oxaliplatin in the treatment of tumors (page 4, paragraph 38). The treatment regime in example 2 teaches the administration of oxaliplatin intravenously on the first day of the cycle and a calcium salt administered orally for days 1-14 to treat tumor cells (page3, paragraph 36). Laine-Cessac et al. teach the intravenous administration of oxaliplatin and a solution of magnesium and calcium salts to treat tumor. It would have been obvious to one of ordinary skill in the art, that both regimes could be applied to treat tumors via treatment with the oxaliplatin active, resulting in the intravenous administration of a solution of magnesium and calcium salts and an oral administration of a calcium salt. The perceived inoperability of the Chazard reference remains because the patient would still receive the cost savings of orally administering the calcium salt at home and would still have the psychological benefits of being within the home environment while taking the medication.

B. Applicant's assert there is nothing in Chazard that teaches or suggests that its compositions produce and reduction of oxaliplatin-mediated neurotoxicity (page 17, paragraph 2 to page 19, paragraph 2 of Applicants' amendment).

Applicant's argument has been fully considered but found not persuasive.

It is the Examiner's position that no matter what time the onset of the neurotoxicity occurred, the administration of calcium and magnesium after the onset of pain dramatically improves the prognosis of the patient. See Laine-Cessac et al. under the time to symptoms onset. The time to the onset of the symptoms was variable for the four patients observed. Patient F/59 did not develop the onset of symptoms until 15 minutes after the end of the treatment infusion, at which time she was promptly administered the calcium and magnesium salt transfusion. Conceivably, within the variability that exists within a patient population receiving this treatment regime, a patient could develop neurotoxicity hours after the administration of the oxaliplatin, at a time when the patient had already left the doctor's office. It would have been obvious to one of ordinary skill in the art at the time of the invention that administration of calcium and magnesium at this time would improve the neurotoxic condition. One of ordinary skill in the art would have been motivated to administer the calcium or magnesium in a non-invasive and safe way, therefore oral administration of the calcium would have been the option of choice. One of ordinary skill in the art would have had a reasonable expectation of success because of the results demonstrated by Laine-Cessac. The presentations of calcium in oral or injectable form are well known to one of ordinary skill

in the art and administering calcium in the forms of partly in an oral form and partly in an injectable form would not be expected to create a differential effect in the body. The prior art by Chazard was intended to demonstrate the fact that an oral form of administration of calcium with oxaliplatin is well known for the treatment of tumors.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOSEPH S. KUDLA whose telephone number is (571)270-3288. The examiner can normally be reached on 9am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Joseph S. Kudla/
Examiner, Art Unit 1611
September 20, 2008

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611